PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/365, 47/36, 9/00, 9/16, A61P 3/04 — A1

(11) International Publication Number: WO 00/09123

(43) International Publication Date: 24 February 2000 (24.02.00)

(21) International Application Number: PCT/EP99/05693

(22) International Filing Date: 6 August 1999 (06.08.99)

(30) Priority Data:

98115310.9	14 August 1998 (14.08.98)	EP
99109430.1	11 May 1999 (11.05.99)	EP

(71) Applicant: F. HOFFMANN–LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH–4070 Basle (CH).

(72) Inventors: BAILLY, Jacques; 8, rue des Pierres, F–68170 Rixheim (FR). FLEURY, André; Kirschweg 25, CH–4145 Gempen (CH). HADVARY, Paul; Neumattenweg 8, CH–4105 Biel–Benken (CH). LENGSFELD, Hans; Marschalkenstrasse 35, CH–4054 Basle (CH). STEFFEN, Hans; Fischmarkt 36, CH–4410 Liestal (CH).

(74) Agent: POPPE, Regina; 124 Grenzacherstrasse, CH–4070 Basle (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS AND CHITOSAN

(57) Abstract

Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary excipients.

B7

11017 U.S. PTO 10/092751 03/07/02

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS AND CHITOSAN

The present invention relates to pharmaceutical compositions containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary excipients.

An example of an inhibitor of gastrointestinal lipases is orlistat, previously known as tetrahydrolipstatin or THL. It reduces the absorption of dietary fat. Its use for the control or prevention of obesity and hyperlipaemia, is described in US patent 4 598 089. Orlistat is the N-formyl-L-leucine ester with (3S,4S)-3-hexyl-4-[(2S)-2-hydroxytridecyl]-2-oxetanone.

Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. It results from physical separation of some liquid unabsorbed dietary fat from the bulk of the fecal mass in the lower large intestine. This effect can be prevented with the pharmaceutical compositions of the present invention.

In the US patent 5 447 953 it has been demonstrated that by combining a lipase inhibitor with substantial amounts of water insoluble crude fibers, the inhibiting effect on fat absorption can be increased.

Surprisingly, it has now been found that by combining the lipase inhibitor with low amounts of chitosan or a derivative or a salt thereof, the phenomenon of anal leakage of oil can be strongly reduced.

The invention is also concerned with the use of chitosan or a derivative or a salt thereof for the combined simultaneous, separate or chronologically spaced use with an inhibitor of gastrointestinal lipases, such as orlistat, in the treatment of obesity and hyperlipaemia and their comorbidities, such as type II diabetes mellitus.

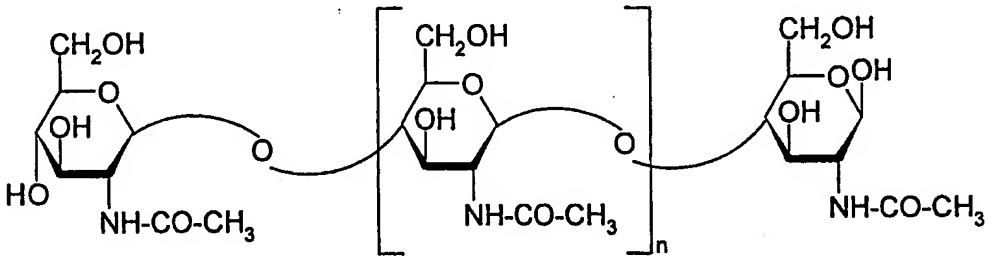
Artificial non-absorbed fats, mostly sucrose polyester, are used in the food industry for the production of low fat foods, such as low fat potatoe chips, low fat

cookies, low fat salad dressings and low fat ice cream. The ingestion of higher amounts of such foodstuffs containing non-absorbable fats can induce oily leakage.

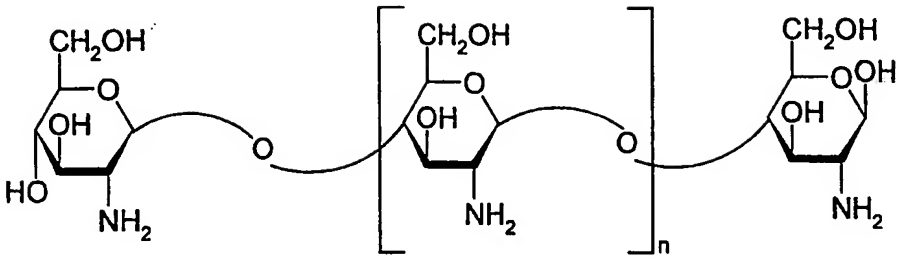
The invention is further concerned with the use of chitosan or a derivative or a salt thereof for treating or preventing the syndrome of anal leakage of oil occurring after the administration of an inhibitor of gastrointestinal lipases, such as orlistat, or after ingestion of food containing poorly absorbable or non-absorbable fats or oils or of undigestible oily fat substitutes.

Chitosan is derived from chitin, a polysaccharide composed of (1→4)-linked 2-acetamido-2-deoxy-β-D-glucopyranosyl residues isolated from natural sources, by complete or partial deacetylation and partial depolymerization. Chitosan has a molecular weight of the order of 10^4 to 10^5. Chitosan is soluble at gastric pH and insoluble or gel-like at intestinal pH. Examples of chitosan derivatives are medium or long chain N-alkyl- or N-alkanoyl-chitosan. The term "medium chain N-alkyl- or N-alkanolyl" refers to C_{8-13}-N-alkyl- or -N-alkanolyl chains, the term "long chain N-alkyl- or N-alkanoyl" refers to C_{14-18}-N-alkyl- or -N-alkanolyl chains. Examples of salts of chitosan are those with acetic, citric, formic and tartaric acid, as well as with diluted mineral acids.

Synonyms of chitosan (the Merck Index, 11th ed., #2052, 1989) are poly-D-glucosamine; poly-[1→4]-ß-D-glucosamine and deacetylated chitin. The deacetylation of chitin which has the formula



to chitosan of the formula



can be performed in hot concentrated NaOH solution (40-50%). Chitosan is commercially available from Pronova Biopolymer, Inc., 135 Commerce Way, Suite 201, Portsmouth, NH03801, e.g. as SEACURE 142, 242 or 342 with a viscosity interior to 20 cps, from 20 to 200 cps and from 200 to 800 cps, respectively.

Examples of auxiliary excipients which can be used in the pharmaceutical compositions of the invention are binders, diluents and lubricants, such as AVICEL, polyvinyl pyrrolidone (povidone), talc and sodium stearyl fumarate; sweeteners, such as sorbitol, glucose, saccharose, saccharine-sodium salt and sodium cyclamate; flavour agents, such as passion fruit, citron and limette; flavour enhancers, such as citric acid, monosodium citrate, sodium chloride and chinine sulfate; effervescing agents, such as sodium bicarbonate and tartaric acid, disintegrants, antimicrobial agents, such as p-hydroxybenzoic acid methyl or propyl ester; detergents and colouring agents, such as β-carotene.

AVICEL essentially comprises microcrystalline cellulose. It is available from FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103, e.g. as AVICEL RC-591 or CL-611, which are mixtures of microcrystalline cellulose (about 92%) and carboxymethylcellulose sodium (about 8%), AVICEL PH 101 or PH 105, which is microcrystalline cellulose with an average particle size of 50 or 20 μ, respectively; AVICEL CE-15 a mixture of microcrystalline cellulose and guar gum.

The superiority of chitosan over microcrystalline cellulose, e.g. AVICEL, in reducing anal leakage of oil is shown in the following experiment:

The experiment for loss of free fecal oil is based on the observation that mice, due to steadily grooming their furs, distribute any excreted free fecal oil all over their bodies. This results in an easily visible brownish coloring of the fur (oily fur greasing). In mice weighing 20-25 g, excretion of free oil was provoked by administering an excessive dose of orlistat (300μmol/kg/day) together with a diet

containing 7% fat, resulting in a daily fat intake of 1 g/day. The diet consisted of mashed Hamburger, butter, French fries and string beans.

The following time schedule of treatment was followed:

days 1-5: feeding groups of 3 mice on the above diet and food additives (increasing doses of chitosan or AVICEL), and a control group without food additives

days 3-4: adding orlistat (300 µmol/kg/day)

day 5: registration by photography of oily fur greasing

Oily fur greasing was evaluated by daily scoring units 1 to 4:

1 representing 0-25% skin involvement, 2: 26-50% skin involvement, 3: 50-75%, and 4: 75-100% skin involvement.

The skin involvement of the individual mice was added up for days 3-5. (At e.g. 100% skin involvement for days 3-5 the scoring would be maximal, i.e. 4+4+4=12 units). The oily fur greasing score in the controls was 6.3±1.6 units (mean ±SE).

In 7 groups of mice receiving chitosan or AVICEL against oily fur greasing, its extent was first evaluated according to the scoring above, then expressed in % of the control groups and finally averaged within the animals of each group. The results are given in the table below:

Oily fur greasing (% of controls) in mice ingesting orlistat (300 µmol/kg/day)

food additive (g/100 g feed)	chitosan	AVICEL
15	n.d.	17±4
10	n.d.	29±7
5	n.d.	53±24
3	6±3	n.d.
1	37±16	n.d.
0.3	53±5	n.d.
0.1	63±9	n.d.

n.d. = not determined

When the diet contained chitosan, the extent of oily fur greasing was reduced. For instance, as compared to controls, the same 53% inhibition of oily fur greasing is obtained with a feed containing as much as 5 weight % of AVICEL and only 0.3 weight % of chitosan.

The compositions of the invention conveniently contain from 10 to 50 , preferably from 20 to 40 parts by weight of chitosan or a derivative or a salt thereof and from 10 to 200, preferably from 20 to 80 parts by weight of auxiliary excipients for 1 part by weight of an inhibitor of gastrointestinal lipase, such as orlistat.

The composition of the invention can also be in form of a commercial pack containing an inhibitor of gastrointestinal lipase and chitosan or a derivative or a salt thereof, with instructions for its use for the simultaneous, separate or chronologically spaced use in the treatment of obesity or hyperlipaemia.

For the treatment or prevention of obesity or hyperlipaemia, a composition of the invention containing from 10 mg to 500 mg of an inhibitor of gastrointestinal lipase, such as orlistat, and from 500 mg to 20 g, preferably from 2 g to 10 g, of an additional compound, such as chitosan, can be administered orally once, twice or three times per day.

The compositions of the invention can be in form of drinkable formulations, such as solutions or suspensions prepared from powder, granules, pellets, tablets to be reconstituted or effervescent tablets; or in form of chewable formulations, such

as tablets, capsules or lozenges. They can also be incorporated into food preparations, such as wafers, crackers or bread, or can be in form of swallowable formulations, such as tablets or capsules.

A preferred composition of the invention is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 120 mg of orlistat and from 0.5 to 5 g of chitosan. Most preferably, the chewable tablet consists essentially of about 60 mg of orlistat and about 2.5 g of chitosan.

A further preferred composition of the invention is a wafer for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 200 mg of orlistat and from 1 to 10 g of chitosan. Most preferably, the wafer consists essentially of about 120 mg of orlistat and about 5 g of chitosan.

A preferred method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprises orally administering orlistat and chitosan in a dosage amount from 10 to 200 mg of orlistat and from 0.5 to 10 g of chitosan per fat containing main meal. Most conveniently, this method comprises orally administering orlistat and chitosan, the dosage amount being from 10 to 120 mg of orlistat and from 2 to 6 g of chitosan, particularly about 60 mg of orlistat and about 2.5 g of chitosan per fat containing main meal.

The following non-limiting examples illustrate pharmaceutical preparations that can be produced by conventional procedures:

Example 1

Chitosan granules or pellets for the simultaneous, separate or chronologically spaced administration of orlistat are prepared as follows:

50 g of chitosan (SEACURE 342) and 50 g of AVICEL RC-591 are mixed and kneaded with demineralized water to a suitable consistency. The wet mass is sieved and then dried in a fluidized bed to give granules. Alternatively the wet mass is extruded and spheronized and then dried in a fluidized bed to give pellets. A quantity of 5 g or 10 g of granules or pellets is filled into sachets as unit dose.

Alternatively, this material is filled into appropriate containers. The dosing may be performed with appropriate spoons.

Example 2

Powder for reconstitution:

Orlistat	0.12 g
Low viscosity chitosan (SEACURE 142)	5 g
Sorbitol	7.11 g
AVICEL CL 611	1.20 g
β-carotene	0.06 g
Citric acid	0.10 g
p-Hydroxybenzoic acid methyl ester	0.15 g
p-Hydroxybenzoic acid propyl ester	0.03 g
Flavouring agent (passion fruit)	0.13 g
AVICEL PH 105	8.00 g
Monosodium citrate	1.00 g
Saccharine-sodium salt	0.10 g
Total	23 g

An oral suspension is obtained by adding tap-water to the above powder to a volume of about 100 ml.

Example 3

Granulates or pellets:

Orlistat	0.120 g
Chitosan (SEACURE 242)	5.0 g
AVICEL PH 101	4.88 g

The above ingredients are mixed and kneaded with demineralized water to obtain a suitable consistency. The wet mass is sieved and dried in a fluidized bed at a temperature below 35°C to give granules. Alternatively, the wet mass is extruded and spheronized and then dried in a fluidized bed to give pellets. A quantity of 10 g the granules or pellets is filled into sachets as unit dose. Alternatively, the material is filled into appropriate containers. The dosing can be performed with appropriate spoons.

Example 4

Effervescent tablets:

Orlistat	0.120 g
Saccharose powder	1.669 g
Low viscosity chitosan (SEACURE 142)	2.5 g
Sodium cyclamate	0.115 g
Saccharine sodium salt	0.004 g
Sodium bicarbonate	0.7 g
Tartaric acid (crystallized)	1.12 g
Sodium chloride (milled)	0.04 g
Chinine sulfate	0.007 g
Flavoring agent	0.025 g
Total	6.3 g

Orlistat, saccharose, chitosan, sodium cyclamate and saccharin sodium are mixed and sieved. The mixture is kneaded with a mixture of ethanol and demineralized water, granulated and dried at a temperature below 35°C in a fluidized bed to give a mixture A. Sodium bicarbonate, tartaric acid, sodium chloride, chinine sulfate and the flavoring agent are mixed and sieved to give a mixture B. A and B are mixed and compressed to effervescent tablets of 6.3 g and a diameter of 30 mm.

Example 5

Chewable tablets:

Orlistat	0.060 g
Chitosan (SEACURE 242)	2.5 g
Sorbitol	1.84 g
AVICEL CE-15	1.0 g
Talc	0.480 g
Sodium stearyl fumarate	0.120 g
Total	6.0 g

Orlistat, chitosan, sorbitol and AVICEL CE-15 are mixed and sieved. Talc and sodium stearyl fumarate are sieved and mixed with the first obtained mixture and then compressed to chewable tablets of 6.0 g and a diameter of 2 cm.

Example 6

Chitosan wafers for the simultaneous, separate or chronologically spaced administration of orlistat are prepared as follows:

Corn flour (5 g) and 5 g of chitosan are mixed. Soybean oil (2 g) is added and the mixture is mixed for 15 minutes. Water is added to form a wet mass which is then extruded. The wet wafers are dried in an oven at 35°C and then packaged.

Example 7

Wafers:

Chitosan	5 g
Soybean oil	2 g
Corn flour	5 g
Orlistat	120 mg

The process is the same as in Example 6 but orlistat is first dissolved in soybean oil and added to the blend. After the wet massing with water and extrusion, the wafers are dried at 35°C.

Example 8

Wafers: the proportions of the ingredients and the procedure are the same as in Example 7, but molten tripalmitin is substituted for soybean oil.

Example 9

Chitosan wafers for the simultaneous, separate or chronologically spaced administration of orlistat are prepared as follows:

Chitosan (5 g) and 5 g of maltodextrin are mixed. Molten tripalmitin (2 g) is added to the mixture. The mass is then wetted with water and the wet mass is extruded. The wafers are dried at 35°C.

Example 10

Wafers:

Chitosan	5 g
Maltodextrin	5 g

Triplamitin	2 g
Orlistat	120 mg

The process is the same as in Example 9 but orlistat is dissolved in molten tripalmitin and then added to the blend. The wafers are dried at 35°C.

Claims

1. Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary excipients.

2. A composition as in claim 1 comprising from 500 mg to 20 g, preferably from 2 g to 10 g of the additional compound(s) and from 10 mg to 500 mg of an inhibitor of gastrointestinal lipases.

3. A composition as in claim 1 or 2 wherein the inhibitor of gastrointestinal lipases is orlistat.

4. A composition as in claim 1, 2 or 3 wherein the additional compound is chitosan.

5. The use of chitosan, its derivatives or its salts for treating or preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of an inhibitor of gastrointestinal lipases, such as orlistat, or after ingestion of food containing poorly absorbable or non-absorbable fats or oils or of undigestible oily fat substitutes.

6. A composition as in claim 3 or 4 which is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 120 mg of orlistat and from 0.5 to 5 g of chitosan.

7. The chewable tablet as in claim 6, wherein the dosage is about 60 mg of orlistat and about 2.5 g of chitosan.

8. A composition as in claim 3 or 4 which is a wafer for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 200 mg of orlistat and from 1 to 10 g of chitosan.

9. The wafer as in claim 8, wherein the dosage is about 120 mg of orlistat and about 5 g of chitosan.

10. A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprising orally administering

orlistat and chitosan in a dosage amount from 10 to 200 mg of orlistat and from 0.5 to 10 g of chitosan per fat containing main meal.

11. The method of claim 10, wherein the dosage amount is from 10 to 120 mg of orlistat and from 2 to 6 g of chitosan, preferably about 60 mg of orlistat and about 2.5 g of chitosan per fat containing main meal.

INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/EP 99/05693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/365 A61K47/36 A61K9/00 A61K9/16 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 12579 A (LANGE LOUIS GEORGE III ;SPILBURG CURTIS A (US)) 1 November 1990 (1990-11-01) page 9, line 12 -page 10, line 23 page 11, line 18 -page 12, line 3	1,3
A	SJÖSTRÖM L, ET AL.: "Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients" THE LANCET, vol. 352, no. 9123, 18 July 1998 (1998-07-18), pages 167-172, XP002123840 ISSN 0140-6736 Methods (pages 167-169) Results: Adverse events (pages 170-171); table 3	1,5,10, 11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1999	08/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat al Application No
PCT/EP 99/05693

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 223 023 A (FURDA IVAN) 16 September 1980 (1980-09-16) column 1, line 1 -column 3, line 2 claims; examples 3,6,7	5

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/EP 99/05693

Box I Observati ns where certain claims were found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 5, 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ..al Application No
PCT/EP 99/05693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9012579 A	01-11-1990	US 5017565 A	21-05-1991
		US 5063210 A	05-11-1991
		AT 114970 T	15-12-1994
		AU 633569 B	04-02-1993
		AU 5535690 A	16-11-1990
		CA 2053258 A,C	21-10-1990
		DE 69014870 D	19-01-1995
		DE 69014870 T	27-04-1995
		DK 469079 T	10-07-1995
		EP 0469079 A	05-02-1992
		ES 2064736 T	01-02-1995
		JP 8019001 B	28-02-1996
		JP 4503813 T	09-07-1992
		US 5484777 A	16-01-1991
US 4223023 A	16-09-1980	NONE	